REMARKS

While, no amendments are introduced in this response, Applicants respectfully request reconsideration of the present application in view of the reasons set forth below.

I. Rejections Under 103 (a)

Claims 1-15 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Topfmeier *et al.*, U.S. Patent No. 4,743,693; Dreckmann-Behrendt *et al.*, U.S. Patent No. 6,166,045; and Rollinger *et al., Eur. J. Pharm. Biopharm.* 53:75–86 (2002). In the pending Action, the Office asserts that the prior art references disclose processes for the preparation of modification I of torasemide, which is a known polymorph, and that the only difference between the prior art process and the present claims is the X-ray diffraction pattern of the torasemide produced by the claimed method (see Office Action, p. 3, paragraph 6). The Office further contends that it would have been obvious to one skilled in the art to prepare crystalline modification I by replication of known conditions for reaching the specific crystalline modification (*Id.*). Because the cited art fails to teach or suggest each element of the claimed invention, Applicants respectfully submit that the Office has failed to establish the obviousness of the claimed invention, and therefore traverse the present rejection.

As acknowledged in the Office Action, to establish obviousness under 35 U.S.C. § 103(a) requires an analysis of the following factors set forth in *Graham v. John Deere Co.*, 148 USPQ. 459 (1966): 1) the scope and contents of the prior art; 2) the differences between the prior art and the claims at issue; 3) the ordinary skill in the art; and 4) evidence of indicating obviousness or nonobviousness. Evidence of nonobviousness includes evidence of surprising and unexpected results.

The present invention relates to a novel process for the preparation of modification I of torasemide. The claimed process differs in that this modification is produced directly from the alkaline extract of the original reaction mixture of a last phase in the synthesis of torasemide. As such, it is simple, cost-effective and provides torasemide modification I directly in a

pharmaceutically acceptable form after a single isolation step and without additional recrystallization steps. In contrast, as shown below, all known processes for the production of modification I involve recrystallization of polymorph II of torasemide in a heterogeneous phase using an organic solvent.

First, Dreckmann-Behrendt *et al.* relates to a different torasemide modification and its production, namely modification III (see title and col. 2, lines 6-10). As such, its primary teachings are irrelevant to the present process, which is directed to production of torasemide modification I. Moreover, Dreckmann-Behrendt *et al.* teaches away from the claimed invention because it discloses that acidification of an alkaline solution comprising either modification I or II of torasemide results only in torasemide modification III (see col. 3, lines 38-54 and col. 5, example 1) and not modification I as claimed herein. Hence, despite any seeming similarities between the prior art process and the claimed process, the processes give entirely different results.

Second, Rollinger *et al.* discloses that torasemide I crystallizes from a hot saturated solution of methanol, ethanol, and propanol by cooling (see p. 77, 2nd column, 1st complete paragraph). Rollinger *et al.* does not disclose the preparation of torasemide modification I from an alkaline extract of an original reaction mixture of a last phase in synthesis of torasemide. In fact, Rollinger *et al.* teaches away from the instant process because it teaches that modification II can be obtained by precipitation of a sodium hydroxide solution of torasemide with an equimolar acetic acid solution at 20 °C (*Id.*). Again, the prior art process gives an entirely different result from the claimed process.

Finally, Topfmeier *et al.* (col. 1, lines 41-49) discloses that modification I of torasemide may be produced by recrystallization of modification II of torasemide. In particular, Topfmeier *et al.* teaches a process of producing torasemide modification I by seeding a suspension of torasemide of modification II in water with very finely divided crystal nuclei of modification I (see col. 2, lines 19-24 and claim 1). Example 3 details this process: crude torasemide is first subjected to a filtration step; then an acid is added to precipitate torasemide, after which

torasemide modification I seed crystals are added to the suspension, followed by heating and rearrangement to produce modification I. Thus, Topfmeier *et al.*, alone or in combination with the other cited references, in no way teaches or suggests that modification I of torasemide may be obtained from the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide.

Indeed, it is clear throughout the prior art that it is modification II which is generally produced, see for example Dreckmann-Behrendt *et al.*, col. 1, lines 44-47: "The modification obtained in the case of the preparation and normal purification by precipitating the torasemide is modification II which usually also results in the case of recrystallizations from other solvents." Likewise, Topfmeier contains the same teaching (see column 1, lines 45-49). Hence, in view of this art, it is surprising and unexpected that torasemide modification I may be produced directly from the alkaline extract of the original reaction mixture without further purification or recrystallization steps.

Because the cited references neither teach nor suggest the claimed methods and because the references themselves evidence the surprising and unexpected results of the claimed methods, the Office has failed to establish the obviousness of the claimed methods. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-15 under 35 U.S.C. § 103(a).

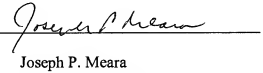
Applicants believe no fees are due with this response; however, the Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

CONCLUSION

For the foregoing reasons, Applicants respectfully submit that the application is now in a condition for allowance. Consequently, Applicants respectfully request the Examiner withdraw the rejection of claims 1-15 and allow the application to issue. If any issues remain to be resolved in view of this reply, the Examiner is invited to contact the undersigned by telephone to achieve a prompt disposition thereof.

Respectfully submitted,

Date September 3, 2008

By 

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